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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/812,113	03/15/2001	K. Roger Aoki	17006CON1	8430

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EXAMINER
CHERNYSHEV, OLGA N

ART UNIT	PAPER NUMBER
1646	6

DATE MAILED: 12/20/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/812,113	Applicant(s) AOKI ET AL.	
	Examiner Olga N. Chernyshev	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4 and 11-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4 and 11-19* is/are rejected.

7)☒ Claim(s) *13 and 17* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of the claims

1. Claims 1 and 4 have been amended, claims 2, 3 and 5-10 have been cancelled and claims 11-19 have been added as requested in Preliminary amendment of paper No.3.

Claims 1, 4 and 11-19 are under examination in the instant office action.

Oath/Declaration

2. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

It does not identify the post office address of each inventor. A post office address is an address at which an inventor customarily receives his or her mail and may be either a home or business address. The post office address should include the ZIP Code designation. The mailing or post office address may be provided in an application data sheet or a supplemental oath or declaration. See 37 CFR 1.63(c) and 37 CFR 1.76.

Claim Objections

3. Claims 13 and 17 are objected to because of the following informalities: The claims do not end with a period. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 4 and 11-19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1, 4 and 11-19 are directed to a method of treating a patient suffering from a neuromuscular disorder, or more particularly from cervical dystonia, by means of administration botulinum toxin type A followed by the administration of botulinum type B. It is disclosed in the instant specification that "a neuromuscular disorder or condition [is] strabismus and other disorders of ocular motility, e.g., comitant and vertical strabismus, lateral rectus palsy, nystagmus, dysthyroid myopathy, etc.; dystonis, e.g., focal dystonias suc as spasmodic torticollis, writer's cramp, blepharospasm, oromandibula dystonia and the symptoms thereof, e.g., bruxism, Wilson's disease, tardive dystonia, laryngeal dystonia etc.; other dystonias, e.g., tremor, tics, segmental myoclonus; spasms, such as spasticity due to chronic multiple sclerosis, spasticity resulting in abnormal bladder control, e.g., in patients with spinal cord injury, animus, back spasm, charley horse etc.; tension headaches; levator pelvic syndrome; spina bifidia, tardive dyskinesia; Parkinson's and limb (focal) dystonia and stuttering, etc." (page 5, lines 20-35 of the instant specification). However, the present specification is not found to be enabling for the claimed method for the following reasons.

According to the modern classification, the term "neuromuscular disorders" is extremely broad and is mostly used to generally describe the disorders that are characterized by the muscular abnormalities caused by dysfunction of muscle enervation. The term "neuromuscular disorders" is so wide-ranging that some modern textbooks and manuals do not use it, replacing it with more precise classification of "Disorders of neuromuscular transmission" or giving the references to the particular disorder or condition, for example, "Muscular Dystrophy" or "Dystonia" (see Merck Manual, pages 1449-1551, 1420-1421). As it is indicated in the instant specification, neuromuscular disorders or conditions can range from Parkinson's disease to stuttering and charley horse (see the earlier quotation). It is obvious to one skilled in the art that all the mentioned earlier disorders and conditions, generally named as "neuromuscular disorders" have different origin, etiology and development. Therefore, one skilled in the art would not expect that the administration of botulinum toxin type A followed by the administration of botulinum toxin type B would lead to the treatment of all possible "neuromuscular disorders" and conditions. Thus, it would require undue experimentation to discover how to practice the present invention as currently claimed.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. In re Wands, 8 USPQ2d, 1400 (CAFC 1988).

As it was indicated earlier, the art of treatment of "neuromuscular disorders" is very unpredictable due to the fact that this definition relates to numerous conditions and syndromes, which differ in their origin as well as progress. The claimed method is drawn to the universal treatment of all possible "neuromuscular disorders", which one skilled in the art would not find predictable or possible. The instant specification does not provide any guidance for a skilled artisan on how to treat "neuromuscular disorders" or conditions with administration of botulinum toxin type A followed by the administration of botulinum toxin type B. The specification fails to support the claimed method by working examples, which would supply one skilled in the art with protocol on how to treat "neuromuscular disorders" with the proposed method. The only working examples of the instant specification describe two patients, one suffering from tardive dyskinesia and one suffering from spasmatic torticollis, which were subjected to the administration of botulinum toxin type A followed by the administration of the botulinum toxin of a different type. In both cases the result of the treatment was such that "the symptoms of tardive dyskinesia continue to be markedly reduced" (page 13, lines 17-18) or "the symptoms [of spasmatic torticollis] continue to be substantially alleviated" (page 15, lines 3-4). It is clear from the presented examples, that the patients suffering form the specific neuromuscular disorders were never cured, but rather the symptoms were reduced or substantially alleviated. Taking into consideration that the specification presents only one example for each described condition, each example contains no description of the route of administration, precise dosage and regime of injection of botulinum toxins, no data supporting the statement of the possible "develop[ing] antibodies" (page 15, line 2) or "neutralizing antibodies" (claims 4 and 16), no explanation on a time course of the treatment or duration of the treatment results and no data on

control studies, one skilled in the art would not have reasons to expect that the proposed method would lead to the treatment of neuromuscular disorders in general or cervical dystonia in particular.

The instant specification fails to provide knowledge of the duration and a reasonable range for the "therapeutically effective amount" of botulinum toxins types A and B. As it is stated on page 11, lines 8-15, "the dosages used in human therapeutic applications are roughly proportional to the mass of muscle being treated" and range from about 80 to about 1,000 units. This information clearly fails to supply the guidance that would be needed by a routine practitioner. The instant specification has also failed to disclose how these parameters are to be determined, how a similar method was practiced in the art with a different agent. In the absence of this guidance a practitioner would have to resort to a substantial amount of undue experimentation involving the variation in the amount and duration of administration of botulinum toxins types A and B of the instant invention. The instant situation is directly analogous to that which was addressed in *In re Colianni*, 195 U.S.P.Q. 150,(CCPA 1977), which held that a "[d]isclosure that calls for application of "sufficient" ultrasonic energy to practice claimed method of fusing bones but does not disclose what "sufficient" dosage of ultrasonic energy might be or how those skilled in the art might select appropriate intensity, frequency, and duration, and contains no specific examples or embodiment by way of illustration of how claimed method is to be practiced does not meet requirements of 35 U.S.C. 112 first paragraph".

Thus, in view of the lack of teachings and unpredictability of the art set forth earlier, and also the lack of the working examples, the instant specification is not found to be enabling for a method of treating a patient suffering from a neuromuscular disorder or from cervical dystonia

by means of administration botulinum toxin type A followed by the administration of botulinum type B. It would require undue experimentation and making a substantial inventive contribution for the skilled artisan to discover how to use Applicants' invention as currently claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1, 4, 11-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claims 1, 4, 12 and 16 are indefinite and ambiguous because it is not clear and cannot be determined form the claims what is "therapeutically effective amount" of botulinum toxins type A and B.

7. Claim 12 is indefinite for recitation of "diminished clinical effectiveness". The degree of the claimed diminution cannot be established from the claim.

8. Claim 14 is indefinite and ambiguous because metes and bounds of the "abnormal head position symptom" are not clear.

9. Claims 14, 15, 18 and 19 are indefinite for recitation of "reduces the severity" or "reduces the neck pain". It is not apparent from the claims how much is the reduction of the severity of the symptoms is intended.

10. Claims 11, 13, 16 and 17 are indefinite for being dependent form the indefinite claims.

Conclusion

11. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Olga N. Chernyshev whose telephone number is (703) 305-1003. The examiner can normally be reached on Monday to Friday 9 AM to 5 PM ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on (703) 308-6564. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-0294 for After Final communications.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)0. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers.

Official papers filed by fax should be directed to (703) 308-4556 or (703) 308-4242. If either of these numbers is out of service, please call the Group receptionist for an alternative number. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. Official papers should NOT be faxed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Olga N. Chernyshev, Ph.D.
December 19, 2001 OC